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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	Gill et al.
Application No.	:	10/069,691
Filing Date	:	June 3, 2002
Art Unit	:	1616
Title	:	Improved Container Composition for Radiopharmaceutical Agents
Docket No.	:	PZ9947 US

Mail Stop Appeal Brief – Patents
Commissioner for Patents
PO Box 1450
Alexandria VA 22313-1450

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APPEAL BRIEF

Sir:

In response to the Notification of Non-Compliant Appeal Brief (37 CFR 41.37) having the mailing date of September 8, 2005, Appellants submit this amended Appeal Brief in triplicate, appealing from the October 26, 2004 final rejection of the Primary Examiner, in which Claims 1-14 were rejected. The Notice of Appeal was filed on April 22, 2005 and the original Appeal Brief was filed on June 21, 2005. Appellants respectfully submit that the enclosed Appeal Brief is now in complete compliance with 37 CFR 41.37(c).

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

Lori Allaire

Signature

Date Sept. 23, 2005

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I. REAL PARTY IN INTEREST

The real party in interest in this Appeal is Amersham plc (now part of General Electric "GE").

II. RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences related to the instant appeal.

III. STATUS OF CLAIMS

Claims 1-14 are pending in this application. The Examiner has rejected all of these claims. Claims 1-14 as amended during prosecution are reproduced in the **Claims Appendix** attached hereto. Appellants are appealing the rejections of Claims 1-14.

IV. STATUS OF AMENDMENTS

Appellants filed an Amendment on December 21, 2004 and an advisory action was mailed on January 18, 2005. No claims were amended subsequent to the Examiner's final rejection that was mailed on October 26, 2004.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Independent Claim 1 describes a composition which comprises a radiopharmaceutical in a container which has a silica coating on the inner surface wherein the radiopharmaceutical includes a metal complex.

Independent Claim 6 describes a kit for the preparation of a sterile radiopharmaceutical metal complex which comprises a non-radioactive organic ligand composition in a container which has a silica coating on the inner surface.

Independent Claim 10 describes a composition for the preparation of a stabilized radiopharmaceutical metal complex which comprises a stabilizer suitable for use with a radiopharmaceutical metal complex in a container which has a silica coating on the inner surface.

Independent Claim 11 describes a composition for the preparation of a sterile radiopharmaceutical metal complex which comprises a bacteriostat suitable for use with a radiopharmaceutical metal complex in a container which has a silica coating on the inner surface.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issues for review in this appeal arise from a Final Rejection that was mailed on October 26, 2004. The Examiner rejected claims 1-14 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,961,952 ("Crane") in view of any one of JP 11099192 ("JP '192") or DE 29609958 ("Schott Glaswerke") or U.S. Patent No. 6,200,658 ("Walther"). Therefore, the issues in this appeal are:

1. Whether Crane in view of JP '192, Schott Glaswerke, or Walther individually or in combination, discloses or suggests all the elements of the following claims:

    a. Claims 1-5,

    b. Claims 6-9,

c. Claim 10, and

d. Claims 11-14?

2. Whether Crane in view of JP '192, Schott Glaswerke, or Walther contain a motivation to combine one reference with the other reference?

VII. ARGUMENT

The Examiner rejected Claims 1-14 under 35 U.S.C. § 103 (a) as being unpatentable over U.S. Patent No. 5,961,952 ("Crane") in view of any one of JP 11099192 (JP '192) or DE 29609958 ("Schott Glaswerke") or U.S. Patent No. 6,200,658 ("Walther").

Furthermore, the Examiner alleges that:
"Clearly, the use of silicon [*Emphasis added*] coated vials is a known advantage in the field of pharmaceuticals and radiopharmaceuticals, and therefore one skilled in the art would obtain these benefits for various pharmaceuticals and/or radiopharmaceuticals, such as, those disclosed by Crane. Therefore the motivation to combine arises from the benefits of the prior art".

Appellants respectfully point out that the Examiner refers to 'silicon' coatings at least 8 times in his Office Action dated October 26, 2004. Such repeated use of this term cannot be explained away as an isolated typographical error. Silicon is the chemical element Si, whereas the present claims refer to silica which is silicon dioxide or SiO_2. Clearly combinations which teach towards silicon coatings teach away from the present invention. The two cannot be treated as interchangeable, since they are chemically very different.

The Board of Patent Appeals and Interferences ("Board") should reverse the Examiner's rejections since Crane in view of JP '192, Schott Glaswerke, or Walther taken as a whole, fails to disclose, teach, or suggest the present invention. Moreover, a proper combination of the references would, at best, teach away from the present invention.

A. The Examiner's Rejections of the Claims Should be Reversed Since Crane, JP '192, Schott Gaswerke, and Walther, Individually or In Combination, Fail to Teach All the Elements of the Claims

The present invention is directed to a composition comprising a radiopharmaceutical metal complex in a container which has a silica coating on the inner surface. The present invention also relates to non-radioactive, preferably lyophilized kits for the preparation of radiopharmaceutical metal complexes, where the kit composition is supplied in a container which has a silica coating on the inner surface.

Crane simply discloses a method of using a metal complex and its analogs to diagnose or radioimage breast tumors. Crane only provides a vague reference to the use of a vial to hold its compounds. More importantly, Crane does not even disclose, teach, or suggest using any type of coating on the inner surface of the vial. Hence, the Appellants respectfully submit that Crane fails to provide any motivation for improving the vial, let along the inner surface for its compounds.

JP '192 discloses that silica-coated vials (prepared by a chemical coating and pyrolysis method), are useful to prevent adsorption of radiopharmaceutical products such as a

thallium chloride, (^{201}Tl), solution to the surface of a glass. JP '192 provides no description of using metal complexes as radiopharmaceuticals. Furthermore, the present invention defines the term 'metal complex' as a coordination complex of a metal (M) with an organic ligand (L). This is to be contrasted with an uncomplexed or free metal ion such as the monovalent thallium cation, Tl^+, used in JP '192.

Schott Glaswerke discloses that glass containers having an internal coating of SiO_2, prepared by a plasma chemical vapour deposition process, are useful for the storage of pharmaceutical or diagnostic solutions. However, Schott Glaswerke provides no further description of a contained material such as radiopharmaceutical metal complexes, let along a radiopharmaceutical, other than the generic reference to 'pharmaceutical'.

Walther discloses a glass tube with an oxide coating. Walther notes that the prior art taught a silica-coated tube for use with (generically) pharmaceuticals. Walther contains no reference to radiopharmaceutical metal complexes per se.

Appellants contend that no motivation to combine exists because Crane itself does not teach or suggest that the radiopharmaceutical metal complexes described therein suffer from any leaching problems, hence no expectation of using silica-coated vial containers exists. Hence, the (unspecified) 'problem being solved' suggested by the Examiner does not exist within Crane itself. Additionally, the Examiner's argument that the secondary references are 'reasonably pertinent to the problem' is vague and not the standard applied by the USPTO for an obviousness attack – which requires motivation based on a clear expectation of improved results for the specific combination be demonstrated.

Appellants also submit that the present invention describes at length how radiopharmaceutical metal complexes suffer from unforeseen or variable problems which are solved using silica-coated vials. See page 4, line 17 to page 9, line 23 of the present specification. None of these problems were recognized in the prior art, and hence the cited references simply cannot provide a motivation to apply silica-coated vials to radiopharmaceutical metal complexes. The solution to the problem provided by the present claims is believed non-obvious for this reason.

Furthermore, the invention as taught by Crane at Columns 7 and 8 has many features: e.g.

tert-butyl Isonitrile ligand
^{99m}Tc or $^{186}Re/^{188}Re$ metal complex thereof
solubilization aid
reducing agent
pharmaceutically-acceptable carrier
a non-radioactive italies-butyl isonitrile metal complex precursor
pharmaceutically-acceptable filler
vial
lyophilization aids
buffers
stabilization aids
bacteriostats
transfer ligand,
etc.

Of all of these features, the Examiner states that it is the *vial* which the person skilled in the art would address to 'improve' on Crane. It is well settled that a reference must be considered not just for what it expressly teaches, but also for what it fairly suggests to one who is unaware of the claimed invention. *In re Baird*, 16 F.3d 380, (Fed. Cir. 1994). The Examiner's reasoning ignores the fact that Crane gives no description, at all, about the inner surface wall of the vial but expounds at length about the other features of the invention. In fact, Appellants respectfully submit, that Crane's inclusion of the vial is not a key contribution to the invention disclosed by Crane. The Examiner fails to demonstrate why one of ordinary skill in the art, upon reading Crane, would be motivated to select the vial – of all things – as the key to 'improving' Crane. Appellants contend that the Examiner has failed to show why the person skilled in the art would select only the vial from this long list of features to seek to improve, and as a consequence choose not to improve all the other aspects even those which Crane teaches as important. Furthermore, why would the person skilled in the art choose specifically silica-coated vials, when a great variety of alternative coatings (e.g. including silicon-containing polymers such as silicones or silanes) were available, in regular use, each also having "benefits". In this respect the Appellants respectfully submit that the Examiner has failed to make a prima facie case of obviousness in rejecting the present invention.

Furthermore, a *prima facie* case of obviousness requires that motivation for the skilled artisan to modify or combine specific references exists. The Examiner's own statements [Office Action, October 26, 2004] refer to "various pharmaceuticals and/or radiopharmaceuticals" and "such as, those disclosed by Crane" and "reasonably pertinent to the problem being solved". These statements, however fail to address the key criterion of why the

person skilled in the art would specifically choose Crane to combine with, and hence where the motivation exists to apply, the silica-coated containers to radiopharmaceutical metal complexes. It is not clear exactly what the specific "benefits" expected for radiopharmaceutical metal complexes would be. The Examiner's own statements seem to suggest that the person skilled in the art *could* apply the silica-coated vials to *any* radiopharmaceutical, of which Crane is merely illustrative. However, to state that one 'could' combine references is not the standard for making a prima facie case of obviousness as such a standard would only grant patentability to combinations which 'could not' be made. Indeed, if the Examiner's logic was followed, then all radiopharmaceuticals would be provided in silica-coated vials, once the cited prior art in question had published, and no one would contemplate using uncoated vials, since it would be folly to ignore the purported 'benefits'. In reality, uncoated vials are still very much the norm for radiopharmaceuticals and coated vials (in any form), the exception. This is because coated vials are significantly more expensive, and no one would accept the additional costs for unspecified "benefits" that were not clearly identified as necessary for the specific product. Accordingly, Appellants respectfully disagree with the Examiner's basis for finding a motivation to combine references.

The Examiner argues that the person skilled in the art would be motivated to combine Crane and JP'192 to solve absorption problems. Crane, however, specifically teaches "solubilization aids" as an essential feature to solve this problem described therein:

Column 2 lines 33-47 and 56-57,
Column 3 lines 23-33 and 46-47,
Column 7 lines 1-26.

The logic of the Examiner's combination is that the 'solubilization aid' taught by Crane would no longer be necessary, since the coated vial would (presumably) solve the absorption problem. This contradicts the teaching of Crane, in that the absence of the 'solubilization aid' would remove an essential teaching of Crane. Accordingly, combining Crane and JP '192 in this manner is an invalid combination.

Additionally, even assuming, *arguendo*, that the references are properly combinable; Appellants respectfully submit that any such combination would teach away from the present invention. 'Teaching away' simply means teaching a solution that would not lead to the claimed subject matter. As noted by the Federal Circuit:

> A reference may be said to teach away when a person of ordinary skill, upon [examining] the reference would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. (emphasis added).
>
> *Para-Ordnance Mfg. v. SGS Importers Int'l*, 73 F.3d 1085 (Fed. Cir. 1995).

Appellants respectfully submit that the mere fact that a reference may suggest an 'improvement' does not dictate that the improvement will direct one to all other 'improvements'. That is, one improvement can teach away from another, as the two improvements may diverge

from each other in their teachings. The *Para-Ordnance* decision (above) clearly states that teaching away does not require a negative teaching in the prior art, the prior art need only teach other, divergent, solutions to be deemed to teach away from an invention.

Thus, by teaching positively towards certain embodiments or features as being important or preferred, the art provides a motivation for the person skilled in the art to go in a particular direction. If that direction leads towards subject matter outside the scope of the claims at issue, then it constitutes a "teaching away". Appellants maintain that the person skilled in the art, even if assumed to be contemplating improvements of Crane, would focus on the specific teachings in Crane of embodiments taught to be important, and be motivated to improve those elements. Crane teaches that a method of using a metal complex and its analog to diagnose or radioimage breast tumors to be important. Again, per *Baird*, it is well settled that a reference must be considered not just for what it expressly teaches, but also for what it fairly suggests to one who is unaware of the claimed invention. *In re Baird supra.* Crane is clearly directed to the use of radiopharmaceutical metal complexes as breast tumor diagnosing or imaging agents, which is described at length from Column 2 line 7 to Column 5 line 21. That is, Crane devotes about four columns of text to what is the essence of his invention, the metal complexes, and not to improved containers for those metal complexes. Again, Crane itself does not discuss the features of the containers used for the compounds, and hence gives no weight to that feature. Crane's emphasis on using metal complexes as breast tumor diagnosing or imaging agents, and the apparent satisfaction with the conventional (ie. uncoated) vial would indicate that improvements to the metal complexes as breast tumor diagnosing or imaging agents are found by

adjusting the formulation of the metal complexes and/or diagnosing or imaging agents, not by modifying the vial.

Accordingly, as none of the cited references are properly combinable so as to render the present invention obvious, Appellants respectfully request that the Board reverse the Examiner's rejections and direct that claims 1-14 be allowed.

B. Claims 1, 6, 10, and 11 are Separately Patentable

Independent claims 1, 6, 10, and 11 are separately patentable from the prior art.

Unlike Crane in view of JP '192, Schott Glaswerke or Walther, claim 1 teaches an improvement of a composition which comprises a radiopharmaceutical metal complex in a container which has a silica coating on the inner surface. Crane does not even disclose, teach, or suggest using a composition in combination with a coating on the inner surface of the vial. Additionally, JP '192 provides no description of using metal complexes as radiopharmaceuticals nor does it disclose, teach, or suggest preparing the silica-coated vials by a plasma chemical vapour deposition (PCVD) process. Furthermore, Schott Glaswerke provides no further description of a contained material such as radiopharmaceutical metal complexes, let along a radiopharmaceutical, other than the generic reference to 'pharmaceutical'. Likewise, Walther notes that the prior art teaches a silica-coated tube that can be used with generic pharmaceuticals but does not disclose, teach, or suggest any reference to radiopharmaceutical metal complexes let along the combination of using silica-coated tubes with radiopharmaceutical metal complexes.

In another light, claim 6 teaches the use of a kit for the preparation of a sterile radiopharmaceutical metal complex which comprises a non-radioactive organic ligand composition in a container which has a silica-coated inner surface. Crane in view of JP '192, Schott Glaswerke or Walther do not even disclose, teach, or suggest using a kit claim for the preparation of a radiopharmaceutical metal complex. use in combination with a coating on the inner surface of the vial.

Additional claim 10 further teaches another use for a radiopharmaceutical metal complex in a container which has a silica coating on the inner surface. Claim 10 discloses a composition for the preparation of a stabilized radiopharmaceutical metal complex which comprises a stabilizer capable of stabilizing said radiopharmaceutical metal complex and an organic ligand which forms a coordination complex with the metal in a container which has a silica coating on the inner surface. Crane in view of JP '192, Scott Glaswerke or Walther do not even disclose, teach, or suggest using the present invention composition claim 10.

Finally, claim 11 teaches yet another use of a sterile radiopharmaceutical metal complex which comprises a bacteriostat suitable for use with a radiopharmaceutical metal complex in a container which has a silica coating on the inner surface. Crane in view of JP '192, Schott Glaswerke or Walther do not even disclose, teach, or suggest using the present invention composition claim 11.

Accordingly, claims 1, 6, 10, and 11 are separately patentable from the prior art.

CONCLUSION

In view of the foregoing, Appellants respectfully request that the Board reverse the rejections of Claims 1-14 as set forth in the Office Action mailed October 26, 2004, that the Board allow the pending claims since they are in condition for allowance, and that the Board grant any other relief as it deems proper.

Dated: September 23, 2005

Respectfully submitted,

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XIII. CLAIMS APPENDIX

1. In a composition which comprises a radiopharmaceutical in a container which has a silica coating on the inner surface, the improvement comprising the radiopharmaceutical includes a metal complex.

2. The composition of claim 1 wherein the radiopharmaceutical is a liquid or solution.

3. The composition of claim 1 wherein the metal of the metal complex is ^{111}In or ^{99m}Tc.

4. The composition of claim 1 wherein the silica coating is deposited by a PCVD process.

5. The composition of claim 1 wherein the container is a glass vial with a closure.

6. A kit for the preparation of a sterile radiopharmaceutical metal complex which comprises a non-radioactive organic ligand composition in a container which has a silica coating on the inner surface.

7. The kit of claim 6 wherein the metal complex is a ^{99m}Tc complex.

8. The kit of claim 6 wherein the non-radioactive organic ligand composition is lyophilised.

9. The kit of claim 6 wherein the silica coating is deposited by a PCVD process.

10. A composition for the preparation of a stabilised radiopharmaceutical metal complex which comprises (i) a stabiliser capable of stabilizing said radiopharmaceutical metal complex; and (ii) an organic ligand which forms a coordination complex with the metal; in a container which has a silica coating on the inner surface.

11. A composition for the preparation of a sterile radiopharmaceutical metal complex which comprises a bacteriostat suitable for use with a radiopharmaceutical metal complex in a container which has a silica coating on the inner surface.

12. The composition of claim 11, wherein the bacteriostat comprises a paraben.

13. The composition of claim 10 wherein the metal of the metal complex is ^{111}In or ^{99m}Tc.

14. The composition of claim 10 wherein the silica coating is deposited by a PCVD process.

IX. EVIDENCE APPENDIX

Appellants hereby append copies of the following patents:

U.S. Patent 5,961,952 by Crane;

English translation of Japanese Patent JP11099192;

English translation of German Patent DE29609958 by Schott Glaswerke; and

U.S. Patent 6,200,658 by Walther.

This is the evidence relied upon by the Examiner for rejection of appealed Claims 1-14 in the Office Action dated October 26, 2004.

X. RELATED PROCEEDINGS APPENDIX

There are no other appeals or interferences related to the instant appeal.

(19) Japanese Patent Office (JP)

(11) Publication Number

11-99192

(12) **Laid Open Patent Publication (A)**

(43) Laid Open 13 April 1999

(51) Int. Cl. [6]
A 61 J 1/00
A 61 K 51/00

Examination Not Yet Requested
Number of Claims 6 (Total 5 pages)

(21) Application Number 9-276593

(22) Filing Date 25 September 1997

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(and one other)

(54) **[Title of the Invention]**

Containers for radiopharmaceuticals and radiopharmaceutical preparations using said containers

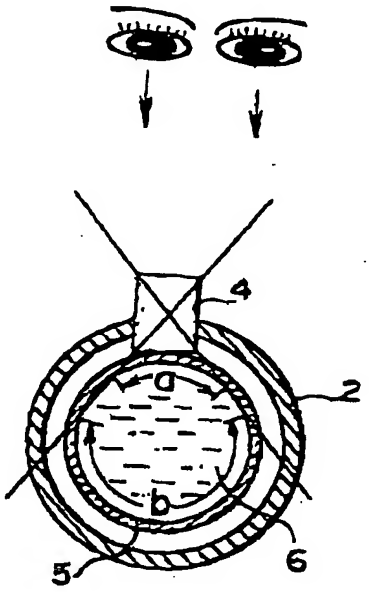
(57) **[Abstract]**

[Purpose]

To develop containers for pharmaceuticals which can prevent highly adsorbable radiopharmaceuticals from being adsorbed thereon and provide a clear description of their contents and the amounts thereof.

[Solution Means]

A container for radiopharmaceuticals in which the interior surface of a glass container is coated with silica and a container for radiopharmaceuticals in which reversed characters are written on the surface of a glass container.



[Claims]

[Claim 1]

A container for radiopharmaceuticals characterised in that the interior surface of a glass container is coated with silica.

[Claim 2]

A container for radiopharmaceuticals characterised in that reversed characters are written on the surface of a glass container.

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[Claim 3]

A container for radiopharmaceuticals according to Claim 2 in which the shape of the glass container is cylindrical.

[Claim 4]

A container for radiopharmaceuticals characterised in that the interior of a glass container is coated with silica and reversed characters are written on the surface of the glass container.

[Claim 5]

A radiopharmaceutical preparation characterised in that a radiopharmaceutical container in which the interior surface of a glass container is coated with silica is filled with an adsorbable radioactive material.

[Claim 6]

A radiopharmaceutical preparation according to Claim 5 in which the adsorbable radioactive material is thallium chloride.

[Detailed Description of the Invention]

[0001]

[The Technical Field to which the Invention Pertains]

The present invention relates to containers for pharmaceuticals which are filled with radiopharmaceuticals and, more particularly, it relates to containers for pharmaceuticals which are filled with radiopharmaceuticals such as radioactive thallium chloride for transport and storage, and containers for pharmaceuticals on which descriptions are printed so that the nature of their contents can easily be confirmed.

[0002]

[The Prior Art]

Radioactive materials are used as tracers for diagnostic imaging in medical fields; in some cases a single element is used as the radioactive material and in other cases they are used by labelling compounds which show specific behaviour *in vivo*.

[0003]

Radioactive materials which are administered orally by means of capsules, etc. or intravenously by injection show *in vivo* distributions specific to the material, and the distributions are detected *ex vivo* using scintillation cameras or gamma cameras. The radioactivities so detected are shown in two-dimensional positional terms and as quantitative distributions; these distributions of radioactivity are grouped by colour using computer processing so giving images of radioactive movement *in vivo*. At present, the use of such techniques enables diagnostic imaging of myocardial disease areas and tumours.

[0004]

With regard to radioactive materials and tracers used for the above-mentioned diagnoses, radioactive thallium chloride as well as radioactive iodine, radioactive technetium, etc. can be cited. Since these radioactive materials are generally used as injections, they are supplied in glass vials or syringe type containers and there has been a desire for precise descriptions of the amounts on these containers so that the required amount of radioactive material can be correctly administered to the patient.

[0005]

However, there is the problem that radiopharmaceuticals such as, for example, radioactive thallium chloride (^{201}Tl) are sometimes adsorbed on the containers and in such cases even when a precise amount is measured, the required amount of the radioactive material cannot be administered to the patient. Although descriptions of the contents and the amounts thereof are usually printed directly on the surface of containers for pharmaceuticals, in the case of containers for radiopharmaceuticals they are often stored in lead-shielded containers equipped with a small lead glass window in order to reduce the exposure of the operators to radiation and it is hard to see the description of the contents and the amount thereof, which is a problem.

[0006]

Attempts have been made to solve the above-mentioned problem of the adsorption of radiopharmaceuticals on their containers by the use of plastic containers (Japanese Unexamined Patent 8-23829), the addition of a reducing agent (Japanese Unexamined Patent 6-256223), etc. Moreover, with regard to methods of describing the contents and the amount thereof, there have been attempts to achieve legibility by using brightly coloured paints, or wide or large characters.

[0007]

However, there are cases in which glass containers are easier to use than plastic containers and the use of reducing agents which are not directly related to the treatment or diagnosis is not desirable. If brightly

coloured paints are used, it becomes difficult to confirm the presence of the actual contents and if a means in which characters are enlarged, etc. is used there is the problem that the characters overflow the small lead glass window so making them illegible.

[0008]

[Problems to Be Solved by the Invention]

There has therefore been a desire for containers for pharmaceuticals which can prevent highly adsorbable radiopharmaceuticals from being adsorbed thereon and can give legible descriptions of the contents and the amounts thereof.

[0009]

[Means of Solving the Problems]

As a result of an intensive investigation by the present inventors in order to solve the above-mentioned problems, it has been found that glass containers whose interior surface is coated with silica can reduce the adsorption of radioactive thallium chloride (^{201}Tl) on the glass surface and they can be used as containers for radioactive thallium chloride injection liquids.

[0010]

Furthermore, it has been found that if a description of the contents, the amount thereof, etc. is written on the outside of the container for the pharmaceutical using reversed characters, the characters are enlarged to give good legibility due to the lens effect of the aqueous solution present inside the container, and furthermore by changing the viewing angle characters can be read over a wide area.

[0011]

That is to say, the present invention provides a container for radiopharmaceuticals characterised in that the interior surface of a glass container is coated with silica. The present invention further provides a container for radiopharmaceuticals characterised in that reversed characters are written on the surface of a glass container. Furthermore, the present invention provides a radiopharmaceutical preparation in which the above-mentioned container for radiopharmaceutical is filled with an adsorbable radioactive material.

[0012]

[Embodiments of the Present Invention]

The container for radiopharmaceuticals of the present invention in which the interior surface of a glass container is coated with silica (hereinafter, termed 'the first container') is prepared by placing a thermally volatile silicone (sic.) compound alone or a solution thereof in an alcohol, etc. inside an ordinary glass container for pharmaceuticals such as, for example, a vial, an ampoule or a syringe and subjecting it to a heat treatment. With regard to examples of the thermally volatile silicone (sic.) compound, silyl tetraisocyanate, silane gases, alkylsilanes, silane alkoxides, silicon halides, etc. can be cited. With regard to detailed methods of coating the interior surface of a glass container with silica, for example, a method disclosed in Japanese Unexamined Patent 2-175630 can be cited. In addition, since glass containers whose interior surfaces

have been coated with silica are commercially available under the product name of Silicoat (made by Fuji Glass Corp.), etc., these may be used.

[0013]

In the first container, the silica film coated on the interior surface of the glass container plays a role in preventing the pharmaceutical solution from coming into contact with water-soluble components such as alkalis included in the glass. That is to say, alkali components such as sodium ions (Na^+) and potassium ions (K^+) are present in the glass, and these components might be dissolved by the pharmaceutical solution. It is believed that in this solution state there is an equilibrium between the potassium ions and the glass; a constant amount of potassium ions is always present in solution, but potassium ions themselves change their state back and forth between the free state and the state in which they are bonded to the glass.

[0014]

When using an aqueous solution containing radioactive thallium chloride (^{201}Tl) as the radiopharmaceutical, since the thallium is present as a monovalent cation and not as a trivalent cation, it can be expected to show the same properties as those of potassium which is a monovalent cation. Since the thallium ions show the same properties as those of potassium ions, the potassium ions and thallium ions react with the glass competitively. As a result, a constant amount of thallium is always adsorbed on the glass. Therefore, even if a precise amount of the radiopharmaceutical is administered to a patient, it is short by an amount corresponding to the

amount of adsorbed thallium and the required amount of the radiopharmaceutical cannot be administered to the patient correctly.

[0015]

When the interior surface of the glass container is coated with silica, the dissolution of potassium from the glass can be suppressed, and thus the equilibrium reaction between thallium and potassium is not caused so preventing thallium from being adsorbed thereon.

[0016]

The container for radiopharmaceuticals of the present invention in which reversed characters are written on the surface of a glass container (hereinafter, termed 'the second container') is one in which reversed characters are written on the side opposite to the viewing side of a transparent container. The reversed characters in the present specification mean those which can be read as normal characters from the side opposite to the surface of the container on which the description has been made and can be read as reversed characters from the surface on which the description has been made.

[0017]

The second container can be obtained by directly printing reversed characters on the surface of a transparent container. It can also be obtained by printing reversed characters on a transparent label and sticking it to a transparent vial. The same effect can also be achieved by printing normal characters on a transparent label, coating an adhesive on the printed surface and sticking it to a glass vial. Furthermore, the same effect can be

achieved by printing normal characters on a non-transparent label, coating an adhesive on the printed surface and sticking it to a glass vial. By thus applying a description it can be read from the side opposite to the printed side.

[0018]

According to the second container, it is possible to enlarge small characters so making them legible by using the refraction of light in the container filled with a liquid and at the same time it is easy to confirm the presence of the contents. When viewing through the lead glass window of a protective container for radiopharmaceuticals in order to avoid direct viewing by the eyes and prevent exposure to radioactive materials, if normal characters are printed on the surface, only the area corresponding to the lead glass window is legible, but when printing is carried out with reversed characters, a wide area becomes legible by changing the viewing angle and furthermore the characters are enlarged due to the lens effect.

[0019]

The effect of the second container is explained in detail by reference to the drawings below. Fig. 1 is a front elevation of a protective container for radiopharmaceuticals and Fig. 2 is a cross-sectional view thereof through line A-A'. 1 is a protective container for radiopharmaceuticals, 2 is the main body of the protective container for radiopharmaceuticals, 3 is the lid of the protective container for radiopharmaceuticals, 4 is lead glass, 5 is the glass container and 6 is a pharmaceutical solution. 2 and 3 are made from an

exposure-preventing metal, generally lead, and it is impossible to see the inside 5 and read characters written thereon through 2 or 3. On the other hand, since 4 is lead glass, it is possible to see the inside 5 and read characters written thereon through 4.

[0020]

Fig. 3 is a sketch showing the range over which characters can be read in each case. When normal characters are written on 5, only the characters on the area corresponding to 4 , that is to say, the area denoted by a, can be read. On the other hand, when reversed characters are written on 5, although it is possible to read them as illegible reversed characters in the above-mentioned area a, characters on the opposite side (diagonal lines) are enlarged due to the lens effect if 5 is filled with a transparent pharmaceutical solution and they can be read as normal characters. By changing the viewing angle relative to 4, characters over a wide area, that is, the opposite area denoted by b, can be read.

[0021]

[Effects of the Invention]

When the first container of the present invention is used as a container for radiopharmaceuticals, in particular a pharmaceutical container for radioactive thallium chloride, by measuring the required amount of radioactive material the precise amount can be administered.

[0022]

According to the second container of the present invention, even when viewing through lead glass, reversed

characters printed on the glass container are enlarged due to the lens effect caused by the container itself and its contents even though it is a small window; by changing the viewing angle a wide area can be read and thus the characters can be easily read.

[0023]

[Embodiments]

Below, the present invention is explained further in detail by reference to examples, but it is in no way limited thereby.

[0024] **Example 1**

Vials for radioactive thallium chloride: The vials of the present invention were obtained by coating the interior surface of 15 glass vials with silica by the method disclosed in an Example of Japanese Unexamined Patent 2-175630. For comparison, 15 glass vials without a silica coating were used (comparative vials). Each vial was filled with 1 ml of an injection solution of radioactive thallium chloride (^{201}Tl) (made by Daiichi Radioisotope Research Centre) and allowed to stand at room temperature for a fixed time so that the thallium could be adsorbed on the glass wall. After that, the solution was discarded, the container was washed with 1 ml of a physiological saline for injection and after discarding the washing liquid the remaining radioactivity of each vial was measured using a solid state detector (made by Seiko EG&G Corp.). The rate of adsorption of radioactive thallium was calculated from the radioactivity remaining relative to the radioactivity introduced. The results are given in Table 1.

[0025]

[Table 1]

Time standing (hr)	Present vial		Comparative vial	
	Radioactivity (cpm)	Adsorption (%)	Radioactivity (cpm)	Adsorption (%)
0.5	1	0.0	1618	6.8
1	5	0.0	1975	8.3
2	1	0.0	1997	8.4
6	2	0.0	2076	9.0
48	1	0.0	2218	11.8

[0026]

From the results above, it was found that adsorption of radioactive thallium chloride on the vial of the present invention coated with silica was greatly suppressed and it could be said to be almost none in comparison with the comparative vial.

[0027] **Example 2**

Vials for elution of radioactive technetium: Normal characters and reversed characters having a width of about 1 mm were written on vials for elution of radioactive technetium (made by Daiichi Radioisotope; diameter 25 mm; hereinafter termed 'collecting vials'). The vial on which normal characters were written was filled with 5 ml of physiological saline and loaded in a shielding container with lead glass (made by Daiichi Radioisotope Research Centre) and it was viewed through the lead glass (normal observation). The vial on which reversed characters were written was also filled with 5 ml of physiological saline and set on diagonal lines relative to the lead glass, and the contents and characters were viewed (diagonal line observation). The results are given in Table 2.

[0028]

[Table 2]

	Size of observed characters	Notes
Normal observation	1 mm	Characters were viewed with no effect from the liquid.
Diagonal line observation	About 1.5 mm	Enlarged characters were viewed due to the presence of the liquid.

[0029]

As is clear from the results above, enlarged characters could be viewed by using reversed characters and carrying out diagonal line observation through the lead glass window, and the presence of a liquid in the container could be confirmed at the same time.

[0030] **Example 3**

5 ml glass vial: A small diameter glass vial (diameter 15 mm: made by Fuji Glass Co., Ltd.) was used as a substitute for a radioactive pre-filled syringe, normal and reversed characters were written on the surface of the vial and the legibility of the characters was tested in the same manner as in Example 2. The results are given in Table 3.

[0031]

[Table 3]

	Size of observed characters	Notes
Normal observation	1 mm	Characters were viewed with no effect from the liquid.
Diagonal line observation	About 2 mm	Enlarged characters were viewed due to the presence of the liquid.

[Brief Explanation of Drawings]

[Fig. 1] Front elevation of a protective container for radiopharmaceuticals.

[Fig. 2] Cross-sectional view of Fig. 1 through line A-A'.

[Fig. 3] Sketch showing the range over which characters can be read.

[Explanation of Numerical Keys]

1 ··· Protective container for radiopharmaceuticals

2 ··· Main body of the protective container for radiopharmaceuticals

3 ··· Lid of the protective container for radiopharmaceuticals

4 ··· Lead glass

5 ··· Glass container

6 ··· Pharmaceutical solution

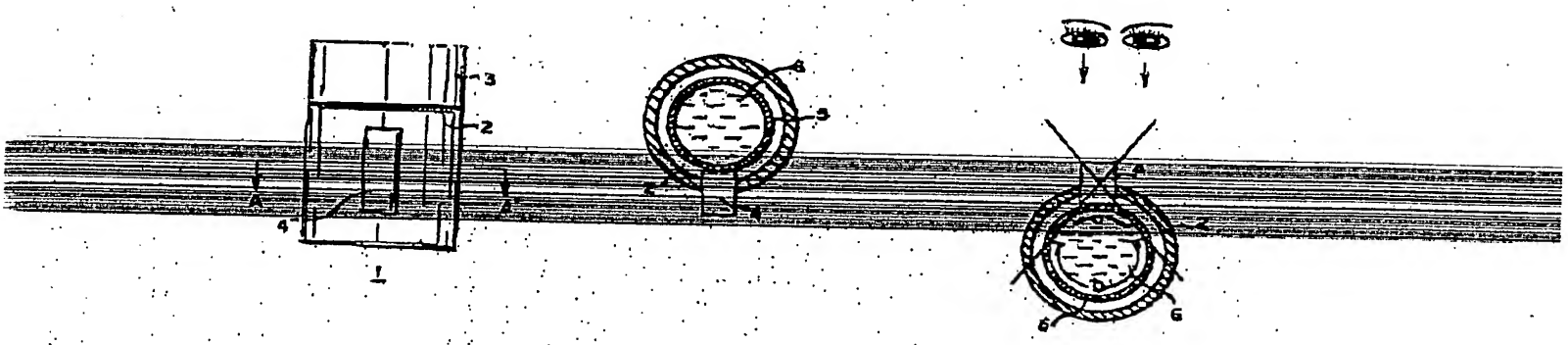
a ··· Range over which normal characters can be read.

b ··· Range over which reversed characters can be read.

Fig. 1

Fig. 2

Fig. 3



Translation of G 1064 and EP 1064

GLASS CONTAINER, SPECIFICALLY FOR THE STORAGE OF PHARMACEUTICAL OR DIAGNOSTIC SOLUTIONS

Background of the Invention

Glass containers for the storage of pharmaceutical or diagnostic solutions are intended to come into direct contact with such solutions. Different types of glass containers are used, such as ampuls, small bottles, injection bottles for prefabricated syringes, cylindrical ampuls and container for the taking of blood and blood samples.

It is known with respect to all glass containers—even glass containers made from borosilicate glass which are classified in the highest quality class in accordance with the pharmacopeias (such as the Deutsches Arzneibuch [German Pharmaceutical Book] DAB 10)—that interactions can be documented between the solutions and the glass surface. However, the interactions in the case of glass containers made from lime-natron glass are even substantially greater.

The interaction is based primarily on the leaching of alkalic substances from the glass surface through the aqueous solution. While the solution is being stored, this leaching can lead to an undesired increase in the pH-value (such as in the case of water for injection purposes) of several pH units (see B. Borchert et al., J. of Parenteral Science & Technology, Vol. 43, No. 2 March/April 1989).

With some medications, it is also possible for a portion of the active ingredient to be inactivated by ions dissolved from the glass, which is particularly disruptive in low dosed medications.

Summary of the Invention

The task of the invention therefore consists of finding a glass container for the storage of pharmaceutical or diagnostic solutions which behaves in a largely inert manner vis à vis these solutions, i.e., a glass container in which the quantity of ions leached from the glass through the solutions is minimized.

This problem is solved by the glass container, specifically for the storage of pharmaceutical or diagnostic solutions, **characterized by the fact,** that the surface which comes into contact with the solutions is coated with a layer of oxides and/or nitrides of the elements Si, Ti, Ta, Al or mixtures thereof applied by means of a plasma CVD process.

Brief Description of the Drawings

Fig. 1 is a sectional view of the container of the present invention.

Detailed Description

The inner side of the glass container, i.e., the surface which is in contact with the solutions, is coated with a layer of oxides and/or nitrides of the elements Si, Ti, Ta, Al or mixtures thereof; said layer is created by means of a plasma CVD process (PCVD process). Specifically, the layer was manufactured by means of the plasma impulse CVD process (PICVD process).

In this process, a layer deposition from the gas phase (chemical vapor deposition = CVD) takes place, and the energy necessary for the cleavage of the precursor gases is brought into the system by means of an electric high frequency plasma. This process is well-known, in and of itself.

Surprisingly, it has been shown that a glass container with layers manufactured according to the PCVD or PICVD process possesses a very extraordinary resistance to leaching and thus behaves in a highly inert manner vis à vis the solutions stored therein.

Oxidic layers are particularly well suited, particularly those made from SiO_2 and TiO_2—with SiO_2 being preferred. The thickness of the layers should be about 10 to 1000 ~~nm~~. A thickness of between 20 and 1000 ~~nm~~, particularly 20 to 500 ~~nm~~, is preferred. It is also possible to deposit multiple layers of varying composition to form a layer package; in this connection, it is intended that the layer package has the aforementioned layer thickness.

The composition of the glass from which the container is made is not critical. In general, the usual clear and colored glass for pharmaceutical applications will be used. Preferred, however, is glass which already belongs to a low hydrolytic class, i.e., particularly so-called neutral glass (borosilicate glass) (DAB 10).

By way of example, Figure 1 shows a 10 ml injection glass bottle. The bottle consists of glass 1, whose inner side is provided with a SiO_2 coat 2. The thickness of the SiO_2 coat is not presented according to scale.

The outstanding properties of the container in accordance with the invention are illustrated by the following example:

A glass container made from borosilicate glass composed of 75% SiO_2, 11% B_2O_3, 5% Al_2O_3, 7% Na_2O, 2% CaO + BaO in the form of an injection bottle with 10 ml capacity, whose inner side has a 150 nm SiO_2 layer applied according to the PICVD process, is filled with 2 ml 0.4 mol HCl and then autoclaved for 1 hour at 121° C. Then the quantity of released sodium, calcium, aluminum, borosilicate and silicate cations is determined in µg/l. For comparison purposes, the test was repeated with an identical container which, however, was not provided with an inner coating. The results are summarized in the table.

	Comparison	
Cations release	Borosilicate glass without layer µg/l	Borosilicate glass with 150 nm SiO_2 layer (µg/l)
Sodium (Na)	3.5	< detection limit of 0.01
Calcium (Ca)	1.1	< detection limit of 0.05
Boron (B)	3.5	< detection limit of 0.10
Aluminum (Al)	2.3	< detection limit of 0.05
Silicone (Si)	5.0	< detection limit of 0.30

Each of the indicated values are average values from 32 tested glass containers. In the glass containers according to the invention, the quantity of leached cations always remains below the detection limit. Particularly surprising is the fact that, in spite of an SiO_2 concentration of 100% in the layer, the leached quantity of Si ions is distinctly lower than with the comparison sample, despite the fact that, in the latter, the SiO_2 concentration in the wall which is in contact with the solution is only 75 percent by weight.

What is claimed is:

1. Glass container, specifically for the storage of pharmaceutical or diagnostic solutions, **characterized by the fact,** that the surface which comes into contact with the solutions is coated with a layer of oxides and/or nitrides of the elements Si, Ti, Ta, Al or mixtures thereof applied by means of a plasma CVD process.

2. Glass container according to claim 1, **characterized by the fact,** that the layer is 20 to 1000 nm thick.

3. Glass container according to claim 1, **characterized by the fact,** that the layer consists of SiO_2.

4. Glass container according to claim 1, **characterized by the fact,** that the layer is applied by means of a plasma impulse CVD process.

ABSTRACT

Glass containers specifically for the storage of pharmaceutical or diagnostic solutions whose surface which comes into contact with the solutions is coated with a layer of oxides and/or nitrides of the elements Si, Ti, Ta, Al or mixtures thereof applied by means of a plasma CVD process.

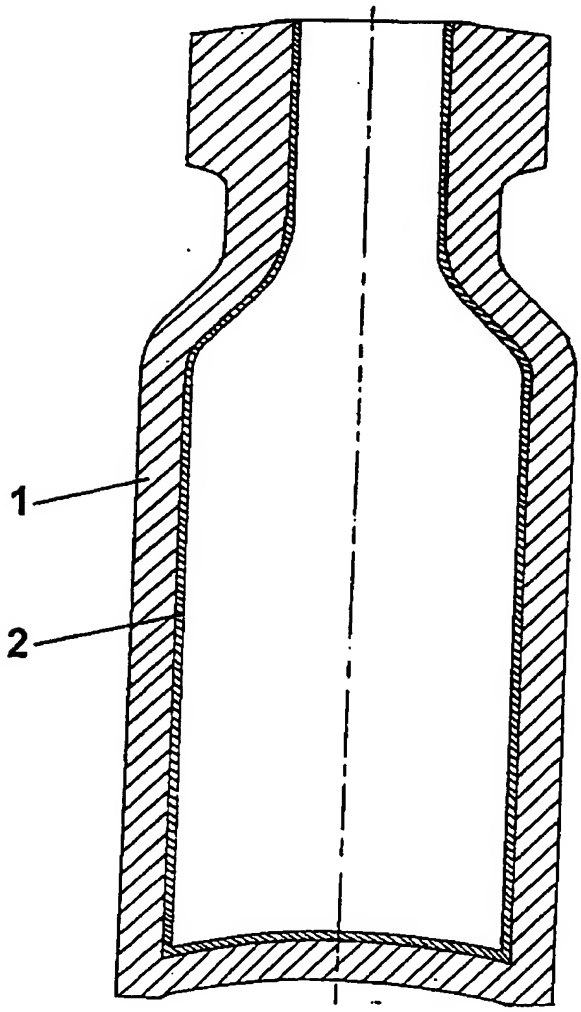


Fig. 1

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